# Personal Experience (off label Use): A New Therapeutic Tool in Various Severe Intoxications


**Prof Patrick Honoré,MD,PhD-Intensivist-Nephrologist,Co-Director of ICU**

**CHU Brugmann University Hospital**

**DMC**

**CHU Brugmann (Reine Astrid)**

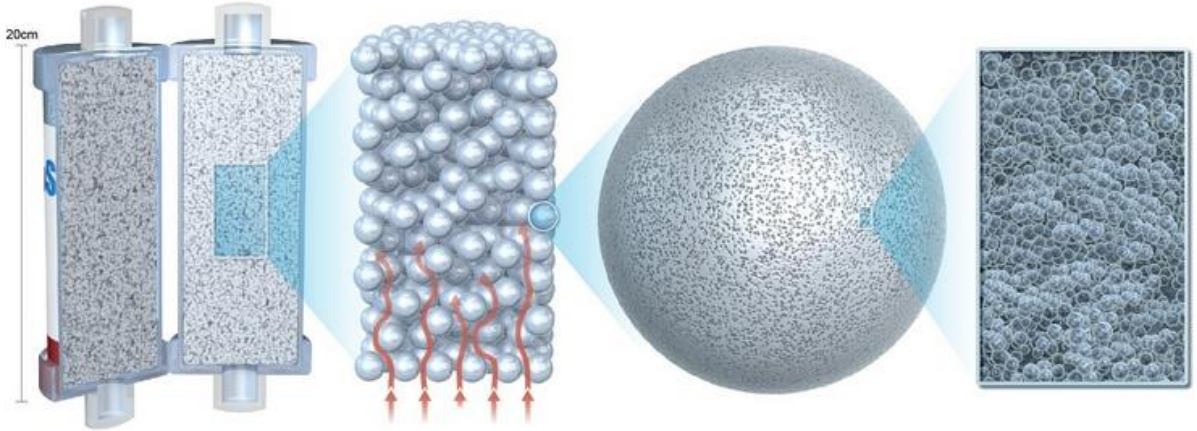

**Paracelsus (1493-1541)**
**'Grandfather of Toxicology'**

**"All things are poison and nothing is without poison, only the dose permits something not to be poisonous."**

**"The dose makes the poison"**

# The CytoSorb Adsorber


- **Highly biocompatible, porous polymer beads**
- **Removal of hydrophobic substances due to**
  - **physicochemical properties**
  - **pore size**




Section through an adsorber | Adsorber bead | Internal structure

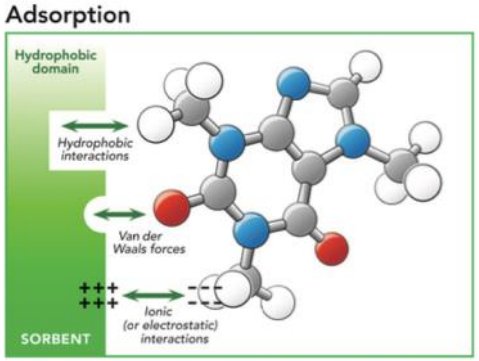
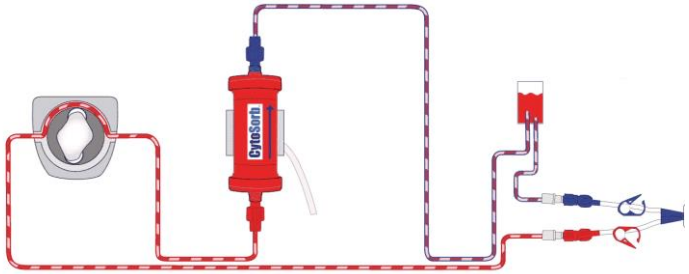
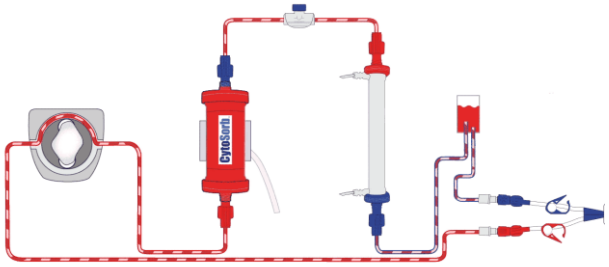



Fig. 3. Adsorption corresponds to the saturable fixation of some molecules directly on a sorbent or a membrane along an affinity gradient depending on ionic, hydrophobic, and van der Waals interactions.

# CytoSorb set-up



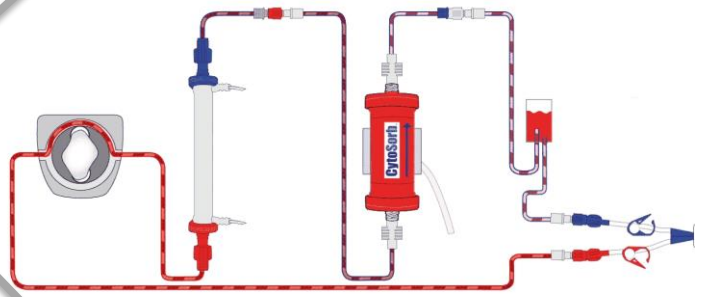

Hemoperfusion




CRRT

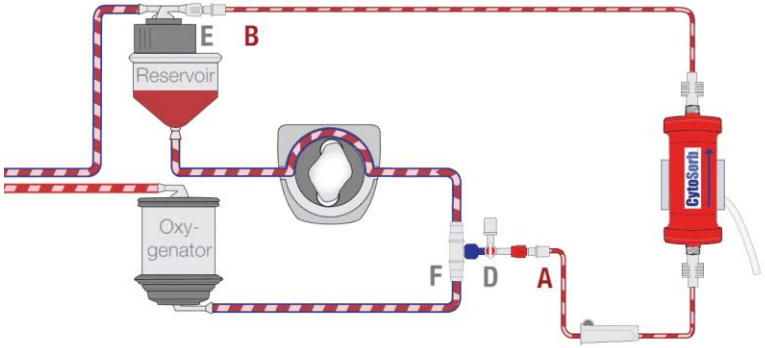
Pre Filter

Post Filter

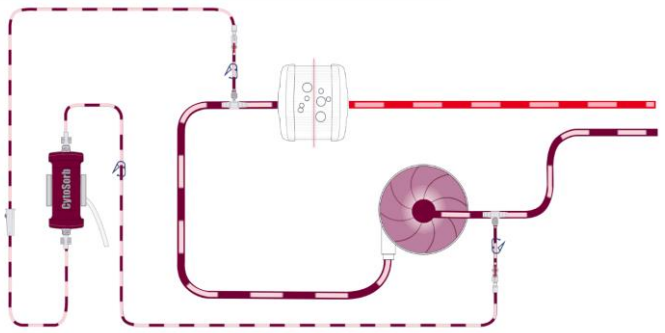



Extracorporeal Circuit

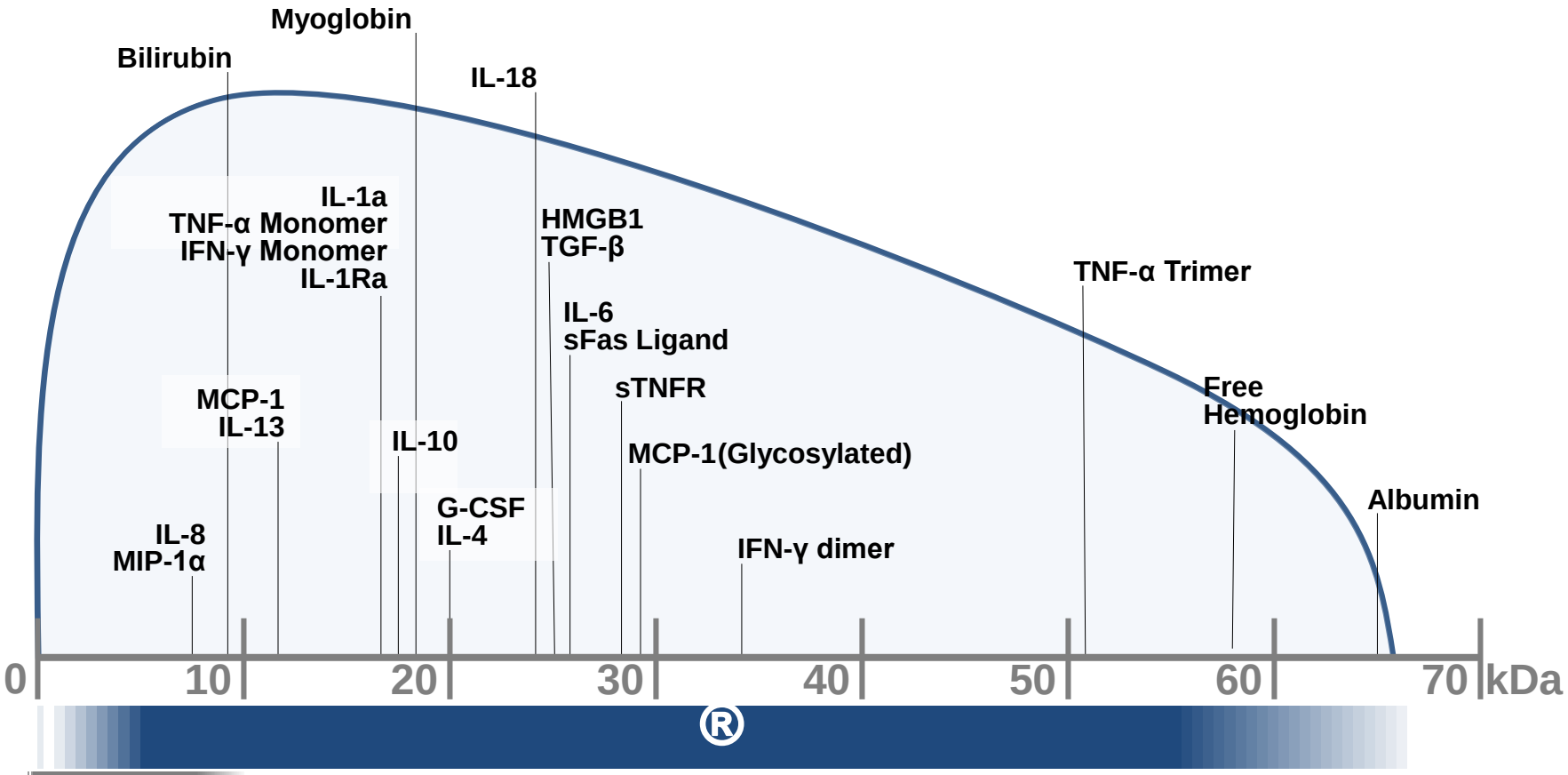
CPB




ECMO



# Adsorber performance - size selectivity




**No elimination of immuno-globulins:**

| | | |
|---|---|---|
| IgG: | | 150 KD |
| IgM: | | 971 KD |
| IgE: | | 198 KD |
| IgA: | Monomer: 160 KD | |
| | Dimer: 385 KD | |
| IgD: | | 172 KD |

# The Surface Defines the Performance

## Membrane-Filter

Overall surface

≅ 2m²

## CytoSorb® – Adsorber

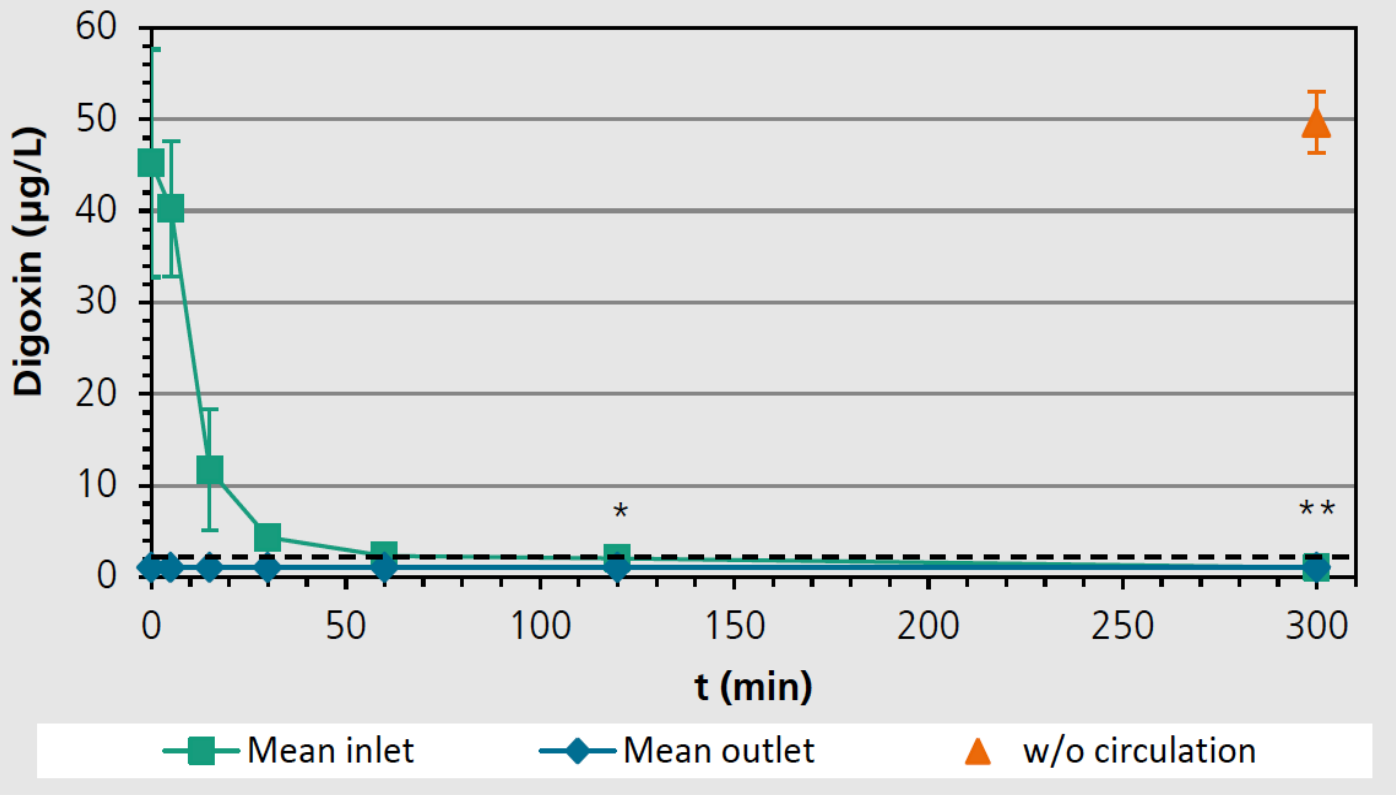
Overall surface

≅ 45.000m²*


| Medication | | | |
|---|---|---|---|
| Amiodarone | | No | Antiarrhythmic agent [D] |
| Digoxin | | Yes | Cardiac glycoside [D] |
| Amlodipine | | Yes | Calcium channel blocker [D, P] |
| Verapamil | | Yes | Calcium channel blocker [D] |
| Diazepam | | Yes | Benzodiazepine [D] |
| Amitriptyline | | Yes | Antidepressant [D] |
| Quetiapin | | Yes | Antipsychotic [P, D] |
| Venlafaxine | | Yes | Antidepressant [C, P] |
| Heparin | | No | Anticoagulant [P] |
| Ticagrelor | | Yes | Platelet aggregation inhibitor [D] |
| Rivaroxaban | | Yes | Anticoagulant (Direct factor Xa inhibitor) [D] |
| Dabigatran | | Yes | Anticoagulant (Direct thrombin inhibitor) [D] |

# REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

Andreas Körtge[1], Steffen Mitzner[1,2], Reinhold Wasserkort[1]
[1]Fraunhofer Institute for Cell Therapy and Immunology IZI, Extracorporal Immunomodulation Unit EXIM, Rostock, Germany
[2] Division of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany




**presented at ESAO congress 2017, Vienna**

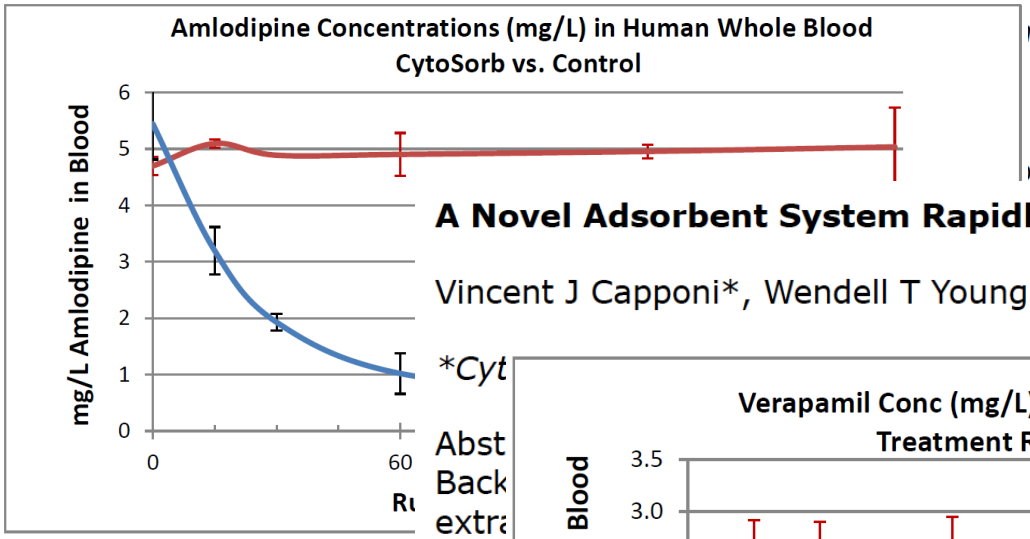
# Removal of Ca – channel blockers-Ex Vivo Studies

**Abstract:**

**A Novel Adsorbent System Rapidly Clears Amlodipine from Human Blood**

Vincent J Capponi*, Wendell T Young*, Eric J Lavonas**, Phillip P Chan*

CRRT
San Diego 2017




...ver, CO

...by current
...al hemoperfusion.

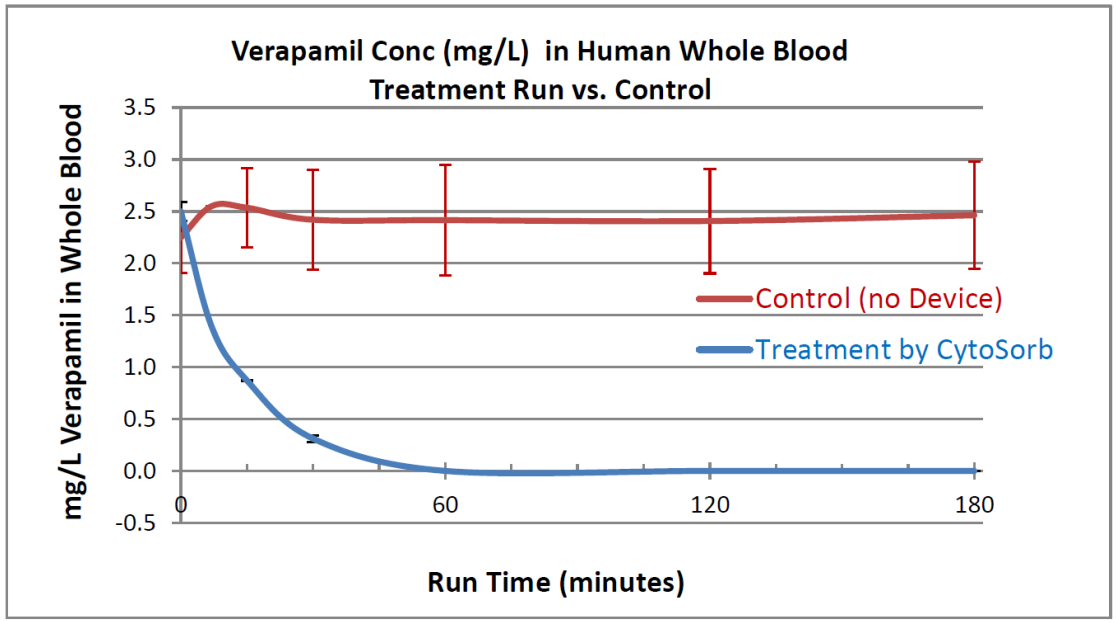
**A Novel Adsorbent System Rapidly Clears Verapamil from Human Blood**

Vincent J Capponi*, Wendell T Young*, Eric J Lavonas**, Phillip P Chan*

*Cyt

Abst
Back
extra
Cyto
marl
Obje
clear

Meth
bloo
Mast
arm,
Who
and




...ent
...perfusion.
...oved and

...an efficiently

...whole human
...Cole-Parmer
...e experimental
...the circuit.
...g equilibration,
...e blood

Whole blood samples we
and after 0, 15, 30, 60,
amlodipine concentration
liquid chromatography m
whole blood. Two experir

verapamil concentrations were determined using previously-validated ultra performance

# REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

Andreas Körtge[1], Steffen Mitzner[1,2], Reinhold Wasserkort[1]
[1]Fraunhofer Institute for Cell Therapy and Immunology IZI, Extracorporal Immunomodulation Unit EXIM, Rostock, Germany
[2] Division of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany

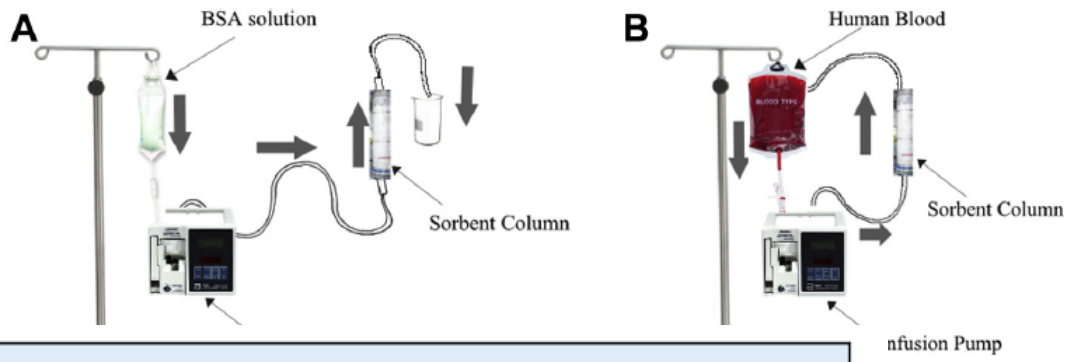
JACC: BASIC TO TRANSLATIONAL SCIENCE


PRECLINICAL RESEARCH

## Ticagrelor Removal Fro

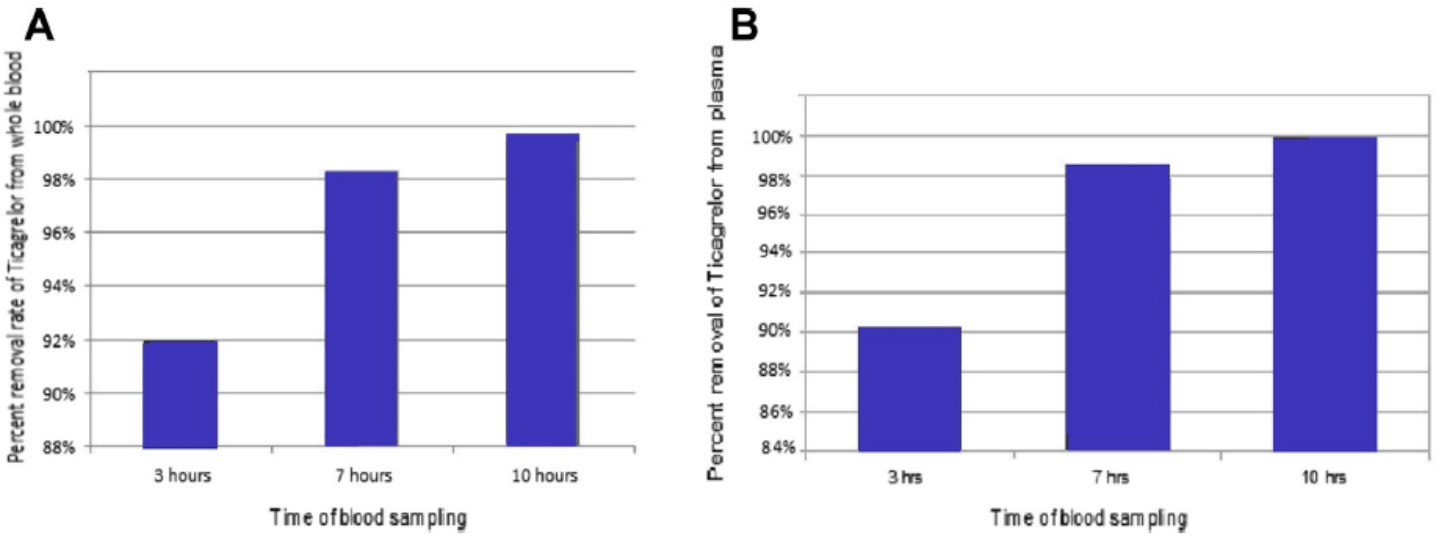
George O. Angheloiu, MD,[a,b,c] Gabriel B. Gugiu, PhD,[d] Cristi
Ramachandra R. Dasari, PhD,[a] Carl Whatling, PhD[f]

**FIGURE 1** Experimental Setup for Ticagrelor Removal From BSA Solution and Human Blood




oumin.

**FIGURE 4** Removal Rate of Ticagrelor From Whole Human Blood and Plasma




Removal rate of ticagrelor from whole human blood **(A)** and plasma **(B)** freshly (<60-min interval until being used) collected during model 3 of the blood recirculating experiment using CytoSorb.

# REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

Andreas Körtge[1], Steffen Mitzner[1,2], Reinhold Wasserkort[1]
[1]Fraunhofer Institute for Cell Therapy and Immunology IZI, Extracorporal Immunomodulation Unit EXIM, Rostock, Germany
[2] Division of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany

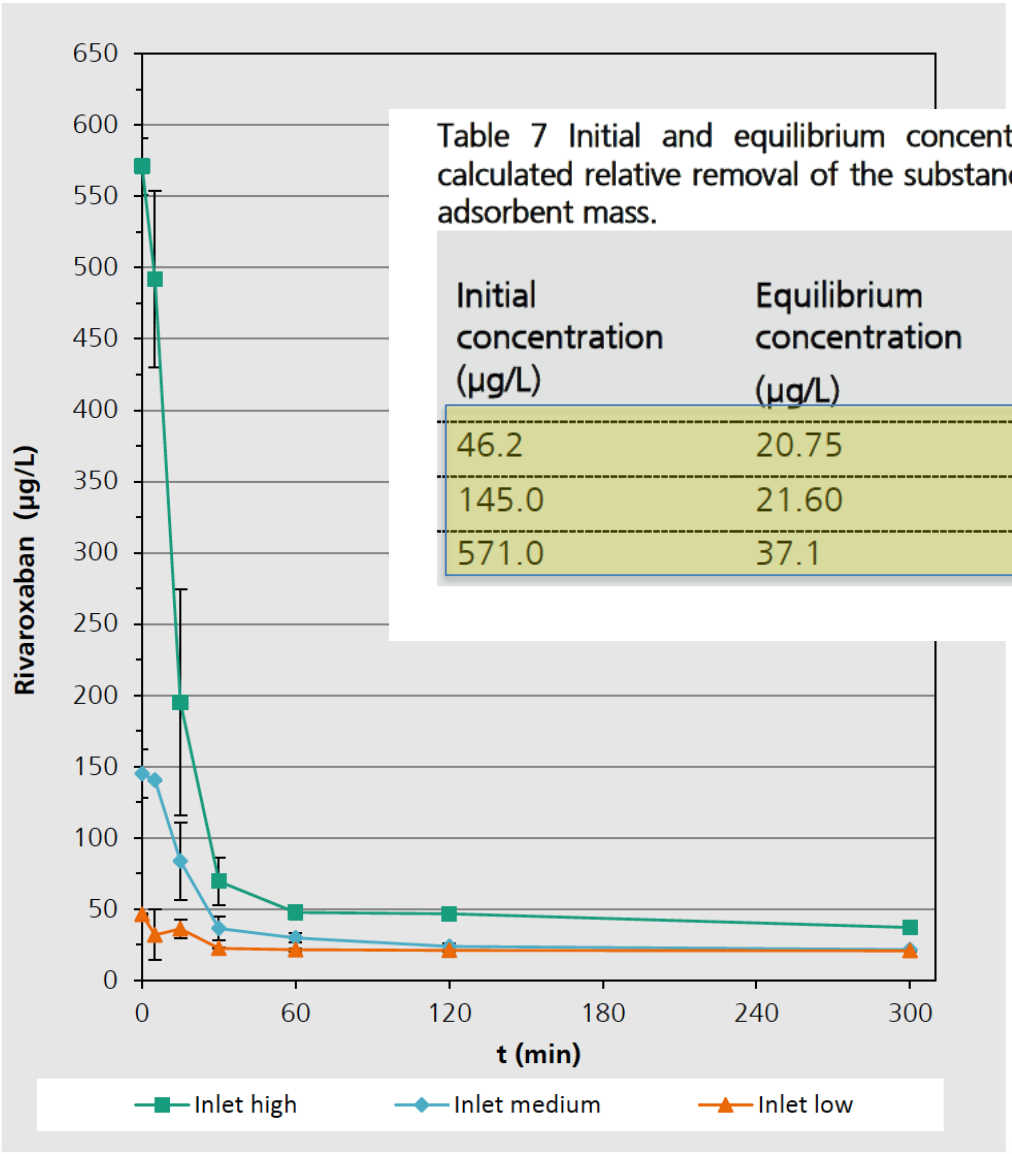
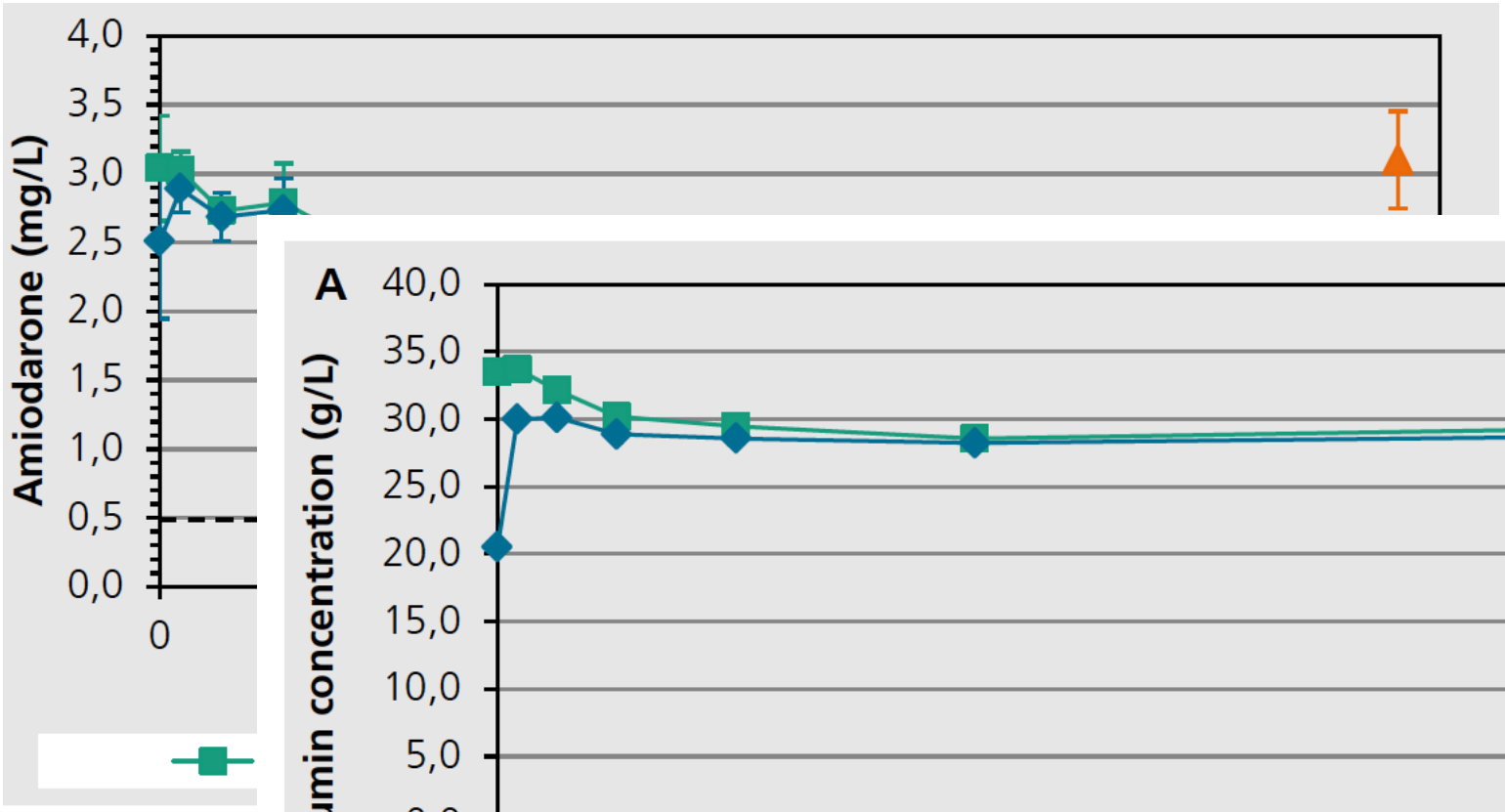



Table 7 Initial and equilibrium concentrations of the Rivaroxaban experiments with the calculated relative removal of the substance from the plasma and the total adsorbed mass per adsorbent mass.

| Initial concentration (µg/L) | Equilibrium concentration (µg/L) | Removal (%) | Total adsorbed mass (µg/g) |
|---|---|---|---|
| 46.2 | 20.75 | 55.1 | 0.42 |
| 145.0 | 21.60 | 85.1 | 2.06 |
| 571.0 | 37.1 | 93.5 | 8.90 |

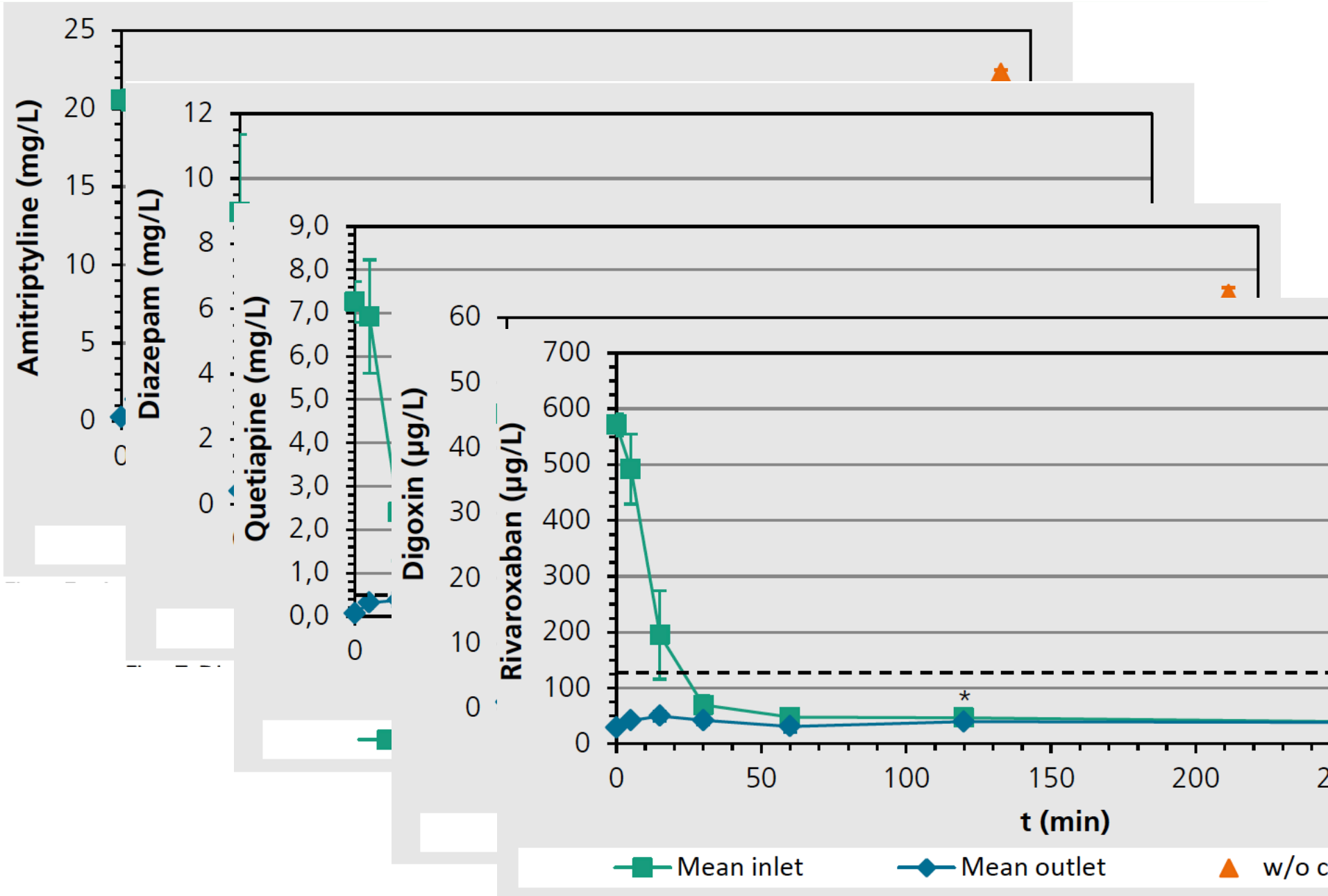
# REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

Andreas Körtge[1], Steffen Mitzner[1,2], Reinhold Wasserkort[1]
[1]Fraunhofer Institute for Cell Therapy and Immunology IZI, Extracorporal Immunomodulation Unit EXIM, Rostock, Germany
[2] Division of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany



# REMOVAL CAPABILITY OF CYTOSORB HEMADSORPTION COLUMNS FOR SELECTED PRESCRIPTION DRUGS FREQUENTLY RELATED TO DRUG OVERDOSE

Andreas Körtge[1], Steffen Mitzner[1,2], Reinhold Wasserkort[1]
[1]Fraunhofer Institute for Cell Therapy and Immunology IZI, Extracorporal Immunomodulation Unit EXIM, Rostock, Germany
[2] Division of Nephrology, Centre for Internal Medicine, University Medicine Rostock, Rostock, Germany



Int J Artif Organs. 2017 Jul 5;40(7):358-360. doi: 10.5301/ijao.5000595. Epub 2017 May 23.

# Venlafaxine intoxication with development of takotsubo cardiomyopathy: successful use of extracorporeal life support, intravenous lipid emulsion and CytoSorb®.

Schroeder I[1], Zoller M[1], Angstwurm M[2], Kur F[3], Frey L[1].

**Young female patient**
**18 g of venlafaxine (240 times the daily therapeutic dose)**

- **Severe cardiomyopathy in a Takotsubo distribution**
- **Cardiogenic shock**
- **MODS**

**Treatment:**

- **Intravenous lipid emulsion**
- **Extracorporeal life support**
- **CytoSorb**

**Outcome:**
**Patient was transferred to the department of psychiatry three weeks after onset of symptoms without somatic residuals**

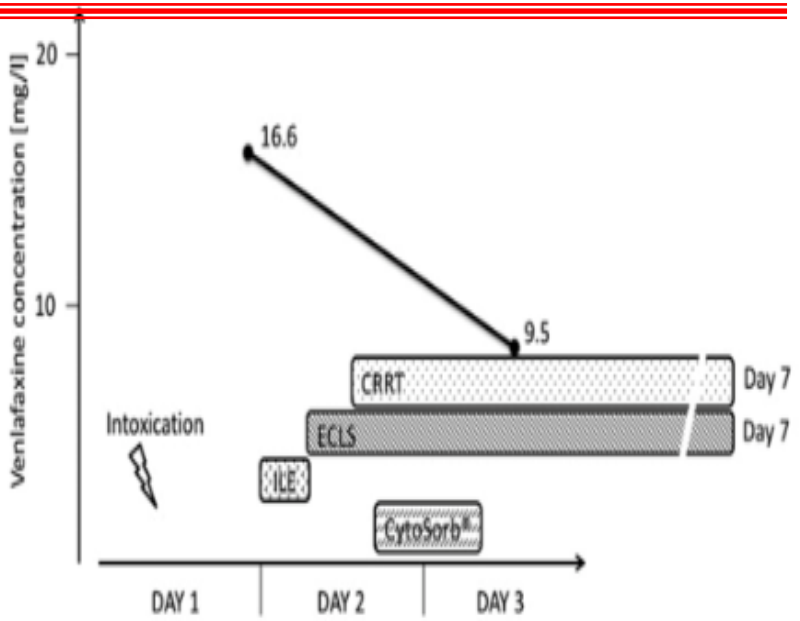



**Fig. 1 -** Timeline showing the key therapeutic interventions during the first 3 days after intoxication with venlafaxine (figure not to scale). Intravenous lipid emulsion (ILE) was started 12 hours after intoxication. Extracorporeal life support (ECLS) was started 13 hours after intoxication. Continuous renal replacement therapy (CRRT) was started 17 hours after intoxication. CytoSorb® was started 32 hours after intoxication. Blood samples for venlafaxine concentration were taken 11 hours and 42 hours after intoxication.

# Case Report

- Lady of 55 years .
- Suicide by massive intake of Tofranil (Imipramine).
- Initial Dosage show > 2,100 mcg/L (Lipophilic Drug)
- Toxic over 500 and lethal > 1,000 mcg/L
- QRS was enlarged up 180 millisec
- Lactate to reduce QRS enlargement
- Intubation (GCS of 6/15).
- Shock :7 Liters of cristalloids in the first 24 hours
- PiCCO monitoring.
- Echo : EF  10 % (Cardiogenic Shock)

# Case Report

- Worsening Shock  2 mcg/kg/min NA ,Dobu15 mcg/kg/min – Adre :1 mcg/kg/min …
- VT, VF, Torsades de pointe.Defibrillations.
- CI with  the PiCCO was 0.3 L/min/M².Cardiac Massage Started.
- Urgent Insertion of VA-ECMO - Femoral access (Flow of 3.5 L/min-Gasflow of 6 )
- Rapid improvement :inotropes could be wean (within 1 hour) -Remaining NA about 0.4 mcg/kg/min.
- Back flow inserted  for the VA-ECMO in the  left groin.

# Case Report

- CVVH (Oligiuria and Rhabdomyolysis) with Cytosorb started within 8 hours.
- Received 3 Cytosorb that were changed every 24 hours.
- Persisting deep coma without sedation (GCS of 3/15) and with myoclonias due to possible brain hypoxia.Bad prognosis.
- Imipramine level went down to 350 mcg/L (<500) at D 4
- VA-ECMO went out at D4 (normal Echo).Lung Improved.
- Ischemia of left limb ; operated for arterial bypass at D 4 with 3 Fasciotomies (Severe Rhabdomyolysis)
- Woke up completely at day 6 with a GCS of 15/15 but was still in MODS with AKI.

# Case Report

- Improvement of the left lower limb at D 10
- The fasciotomies were closed at D 10
- Extubation at D 10
- CVVH was stopped at D 14
- Right lower pneumonia  due to influenza infection.Tamiflu and high nasal flow oxygen
- She was discharged at D 16  to the normal ward.
- At D 25 back home and can walk by herself.

# Conclusions – Take home messages

1) Cytosorb safety (> 50,000 applications,no adverse events), effective in removing inflammatory mediators , easy to use…

2) Removal of highly albumin bounded drugs with high Vd

3) Concentration dependent: Right Timing!

3) Removal of different drugs is possible: Antidepressors (Venlaflaxine, Tricyclic andidepressant,), Cardiac Glycoside (Digoxin), Platelet agreggation inhibitors (Ticagrelor) NOACs (Rivaroxaban; Dabigatran), Calcium Channel Blockers (Verapamil,Amlodipine)

4) Can be Life Saving under these conditions